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ONTOGENY OF GROWTH HORMONE (GH), INSULIN-LIKE GROWTH FACTORS (IGF-I AND IGF-II) AND IGF BINDING PROTEIN-2 (IGFBP-2) IN GENETICALLY LEAN AND OBESE SWINE[1,2]

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ABSTRACT

Serum GH, IGF-I, IGF-II and IGFBP-2 concentrations were determined by radioimmunoassay in swine of genetic lines which were selected for high (obese) and low (lean) backfat. Blood samples were collected at birth, before and after nursing, at 1 and 3 days of age and at weekly or fortnightly intervals until 30 weeks of age. Overall, GH, IGF-I, IGF-II and IGFBP-2 were highest at birth and declined during the first week of postnatal life. An age-by-line interaction was apparent for GH and IGF-I during the early neonatal period with levels being higher in the lean line than the obese line at 1 day of age and similar at 1 week of age. At 3 to 5 weeks of age there was an elevation in GH which was greater in lean than obese pigs. IGFBP-2 concentration patterns were characterized by a nadir at 5 to 7 weeks of age and a decline from an apex at 8 weeks of age in both lines. IGF-II declined steadily from birth until about 10 weeks of age. A subsequent increase in IGF-II was then observed between 12 and 22 weeks, which was greater in the obese line and in male pigs but not apparent in lean females. At birth, pigs which had not nursed had higher GH and IGFBP-2 and lower IGF-I and IGF-II concentrations. The effect of nursing on IGF-I was significantly influenced by line. These data indicate that the endocrine milieu and developmental changes in the endocrine milieu of pigs with differing propensities for obesity differs, suggesting that there is an association between growth factors and physiological traits such as the development of obesity.

INTRODUCTION

Developmental changes in circulating growth factor concentrations and/or their binding proteins have been well characterized in the fetal and neonatal rat (1,2) and to a lesser degree in sheep (3,4), cattle (5) and swine (6,7,8). Growth hormone (GH) is a major coordinator of normal body growth and metabolism. Its lipolytic actions inhibit growth of adipose tissue, while its somatogenic actions stimulate lean tissue deposition. Many of the somatogenic actions of GH are exerted through stimulation of the production of IGF-I and possibly IGF-II. Biological activity and half-life of IGF-I and IGF-II are modulated by specific high affinity IGF-binding proteins (IGFBPs). Porcine serum contains at least five IGFBPs (8). Elucidation of developmental patterns of circulating growth factors in animals with differing propensities for obesity may partially explain the differences in patterns of growth.

Genetically lean and obese lines of swine have been developed by selection for and against fatness [(9, see Mersmann (10), for review]. Animals of these lines demonstrate differing rates of maturation during fetal development (11). These differing rates of prenatal maturation are evident in body composition, circulating concentrations of hormones, serum proteins, and metabolic products at 110 d of gestation. Postnatally, pigs of the lean line grow at a faster rate and their carcasses at maturity are composed of considerably more protein

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and less fat (12,13). Althen and Gerrits (14) measured greater concentrations of GH in pigs of the genetically lean versus obese lines; however, differences in half-life, metabolic clearance rate and GH secretion rate were not observed between the two genotypes (15). Pigs of both lines appear to be without gross dysfunctions in metabolic systems, e.g., carbohydrate and/or lipid metabolism. Animals of the two lines have similar values for circulating glucose, triglycerides, cholesterol, and insulin (16). Pigs of the lean line have more adipocytes per gram of adipose tissue than those of the obese line (17). However, adipocytes of the obese pigs are larger, have more lipogenic capacity and activity of acetyl CoA carboxylase is greater (17).

Possible differences in the ontogenic patterns of circulating concentrations of IGF-I, IGF-II, and IGFBPs have not been reported in genetically lean and obese pigs. The present study was initiated to quantitate changes that occur in these growth factors from birth to maturity in pigs of both sexes and genotypes.

MATERIALS AND METHODS

Pigs of lean and obese lines (9) which had been selected solely for backfat thickness were used in this study. These lines were developed by selection in Yorkshire and Duroc swine for 14 or 18 generations respectively, for high (obese) or low (lean) backfat thickness. Subsequently, the Yorkshire obese and Duroc obese lines were crossed, and the Yorkshire lean and the Duroc lean lines were crossed to produce composite lines of lean and obese swine. Animals were subjected to standard husbandry procedures and maintained in modified environment buildings at the U.S. Meat Animal Research Center (MARC, Clay Center, NE). Blood samples were collected by venipuncture of the descending vena cava or jugular vein. Immediately after collection the blood samples were placed on ice for transport to the laboratory. The blood samples were allowed to clot for 3 hr and centrifuged. Serum was then harvested, frozen and kept at -15°C until assayed. Porcine GH concentrations were quantitated using a double antibody radioimmunoassay (RIA,18). Serum concentrations of IGF-I and IGF-II were determined by specific RIA (19,20). The IGFBP-2 analysis was completed using a heterologous RIA described previously (8). The antisera utilized was raised against bovine IGFBP-2 (bIGFBP-2, 97% pure by HPLC) and provided by Dr. D.R. Clemmons (8). Fetal porcine serum quantitated against purified porcine IGFBP-2 isolated from porcine vascular smooth muscle cell-conditioned medium was used as the standard and bIGFBP-2 was used as the radioiodinated ligand (8). Recovery of pIGFBP-2 added to normal porcine serum as the standard fetal porcine serum was 102% (SE = 2%) in the RIA. Serial dilution of pig sera was parallel to the standard curve between 0.5 and 5 µl. Intra-assay variation was 6%, 10%, 11%, and 8% in the GH, IGF-I, IGF-II, and IGFBP-2 RIA respectively. All samples for a specific RIA were measured in a single assay in order to avoid interassay variation.

Study 1. *Zero to 6 weeks of age* Pigs used were born during the last two weeks of December, 1988 and in January, 1989. The study consisted of 20 lean males, 23 lean females, 22 obese males and 24 obese females. Fifteen litters of lean pigs and 13 litters of obese piglets were sampled. Blood samples were collected on the day of birth, at 1, 3, and 7 days of age, and weekly from 2 to 6 weeks of age. On the day of birth some piglets were sampled before they had nursed. Piglets remained with dams until 4 weeks of age, at which time they were weaned and moved to a nursery facility. In the nursery the pigs were fed a standard corn-soybean nursery ration containing about 18% crude protein.

Study 2. *Five to 30 weeks of age* Pigs were born during the last two weeks of December, 1987 and in January, 1988. Nineteen males and 10 females from 11 litters of lean pigs were sampled. Ten males and 12 females from 12 litters of obese pigs were sampled. Sampling began about one week after pigs had been weaned and moved to the nursery. At 8 to

9 weeks of age the pigs were transferred to a growing-finishing facility for the remainder of the study. The diet offered in the growing-finishing facility was a standard corn-soybean grower ration containing about 16% crude protein. Blood samples were collected at approximately weekly intervals from 5 to 8 weeks of age and at fortnightly intervals from 10 to 30 weeks.

Statistical Analysis. The *a priori* decision was to perform separate analyses for each endocrine measure for the day of birth samples, samples collected from 1 day to 6 weeks of age, and samples collected from 5 weeks to 30 weeks of age using General Linear Models procedures of the Statistical Analysis System (21). Hormone concentrations across age were analyzed by split-plot analysis of variance. Models included line or genotype, sex, and resulting interactions tested by animals within line by sex•group as the whole plot error term. The effects of age and interactions with line and sex tested by residual error comprised the subplot portion of the analysis. Day of birth samples were excluded from these analyses. Least-squares means and standard errors for effects of line by age, sex by age and line by sex by age were obtained. The data from samples obtained on the day of birth were analyzed in a model which included line, sex, nutritional status (nursed or not nursed) and resulting interactions. Least-squares means and standard errors for effects line by nutritional status, sex by nutritional status and sex by line by nutritional status were obtained.

RESULTS

Effects of age and line. Figure 1 presents the age associated changes in serum concentrations of GH, IGF-I, IGF-II, and IGFBP-2 by line. Data from the two studies are presented in the same panels. Significant ($P<.05$) age by line effects were noted for GH, IGF-I, IGF-II and IGFBP-2 concentrations in both studies, 0 to 6 and 5 to 30 weeks of age, in lean and obese swine. Influence of sex or interaction of sex and age was not significant ($P > .05$) in

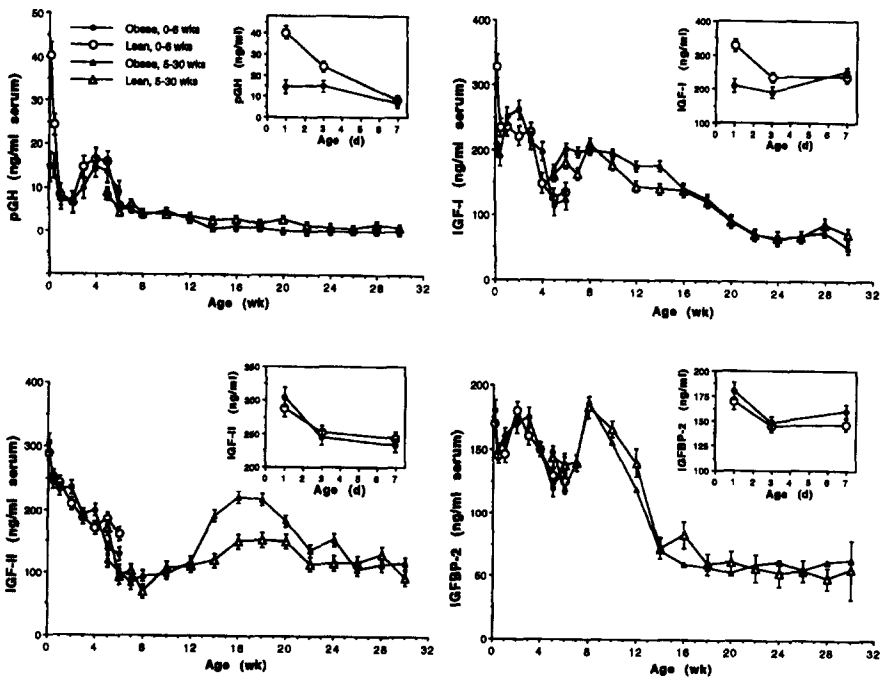

Figure 1. Concentrations of pGH (top left), IGF-I (top right), IGF-II (bottom left), and IGFBP-2 (bottom right) in lean (n=43) and obese (n=46) piglets from 1 day to 6 weeks of age and in lean (n=19) and obese (n=22) from 5 to 30 weeks of age. Inserts present the data for 1 to 7 days of age. Values are LS means ± SE.

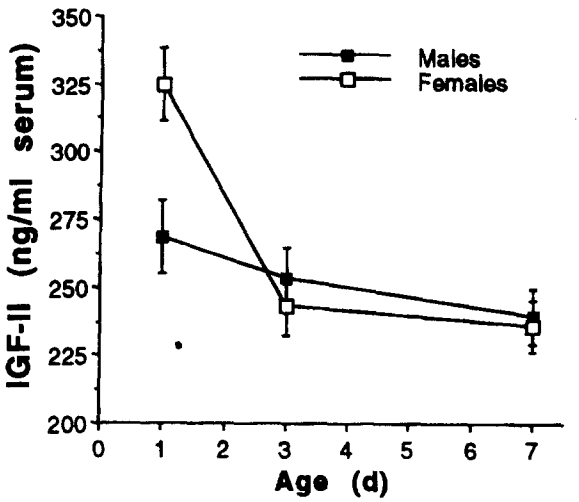

Figure 2. Concentrations of IGF-II in lean and obese males (n=42) and lean and obese females (n=47) during the first week of postnatal life. Values are LS means ± SE.

either study. During the early neonatal period (birth to 7 days of age) there were considerable changes in concentrations of GH, IGF-I, IGF-II and IGFBP-2. This period has been expanded and presented in the inserts in Figure 1 (data for the first week were not statistically analyzed separately since analysis of *a posteriori* selected portions of the data would not be valid). Overall, circulating concentrations of GH, IGF-I, IGF-II and IGFBP-2 were highest at birth and declined during the first week of postnatal life. An age-by-line interaction during the first week of postnatal life is suggested for GH and IGF-I, as circulating levels of both growth factors were higher in lean pigs than obese pigs shortly after birth and were equivalent in the two lines by 7 days of age. Examination of the serum IGF-I concentrations in the obese pigs during this period indicated that circulating IGF-I concentrations increased during the first few days postnatally. In addition, there appeared to be an effect of sex on the age-related decline in serum IGF-II during the first week. Serum IGF-II levels were higher in female than male pigs at 1 day of age and declined more abruptly thereafter such that by day 7, serum IGF-II concentrations were equivalent in both sexes (Figure 2).

Following a precipitous decline from birth to week 2 of postnatal life, serum GH levels increased sharply in both genotypes between 3 and 5 weeks of age (Figure 1). This increase in circulating GH concentrations tended to be associated with a decrease in serum IGFBP-2 levels (Figure 1). Serum levels of IGF-I and IGF-II decreased from the concentrations measured immediately following birth, but remained high overall (Figure 1). Although not different between lines, the elevation in serum GH levels between weeks 3 and 5 was greater in male than female pigs (Figure 3).

Significant ($P < .05$) age-by-line effects were noted for all parameters in the postweanling pigs from 5 to 30 weeks of age. Circulating GH and IGFBP-2 concentrations decreased with advancing age in both genotypes of pigs. Serum GH levels gradually declined during the period of 5 to 13 weeks of age, and subsequently remained low for the duration of the study, until 30 weeks of age. Circulating IGFBP-2 levels declined sharply from an apex at 8 weeks and until 18 weeks of age after which they remained low through 30 weeks of age. Circulating IGF-I concentrations were greater in obese pigs than lean pigs between 5 to 14 weeks of age, but were similar between lines thereafter. Concentrations of IGF-II were elevated between 12 and 22 weeks of age in both lines of pigs. However, this transitory elevation of IGF-II was greater in the obese line than the lean line of pigs. Examination of individual line by sex groups revealed that this elevation in IGF-II was lowest in the lean females, and

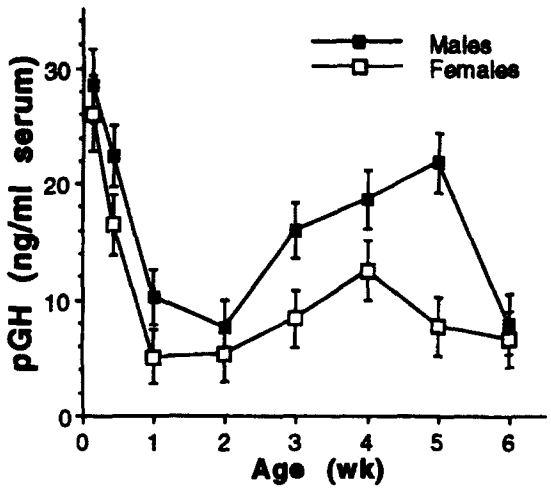

Figure 3. Effect of sex on pGH concentrations in lean and obese males (n=42) and lean and obese females (n=47) from 1 day to 5 weeks of age. Values are LS means ± SE.

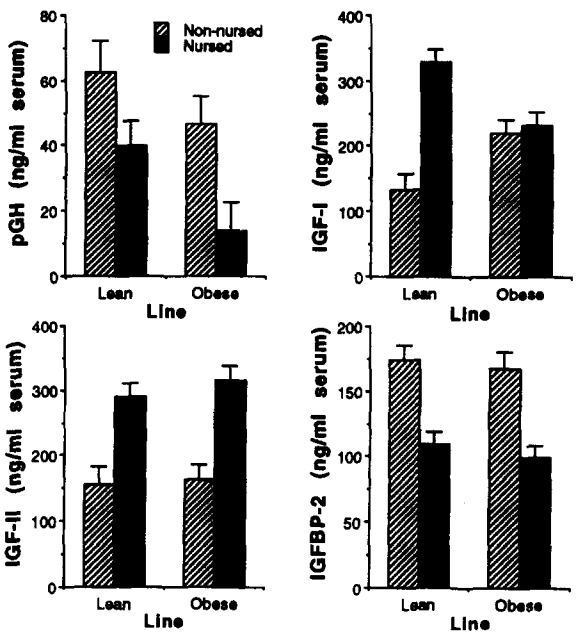

Figure 4. Concentrations of pGH (top left), IGF-I (top right), IGF-II (bottom left), and IGFBP-2 (bottom right) in lean and obese, non-nursed (hatched bars) and nursed (solid bars) piglets on the day of birth. The number of pigs sampled were 24 non-nursed and 16 nursed from the lean line, and 23 non-nursed and 20 nursed from the obese line. Concentrations of GH were influenced (P<.05) by effects of line and nursing, IGF-I concentrations were influenced by interaction of line and nursing and IGF-II and IGFBP-2 concentrations were influenced by effect of nursing. Each bar represents LS means ± SE.

less in lean males than in obese animals of either sex (data not shown). There was an interaction (P = .06) of age and sex for IGF-II.

Effect of nursing. Blood samples were taken on the day of birth from pigs which had nursed and pigs which had not nursed. Nursing had a significant influence on GH, IGF-I, IGF-II and IGFBP-2 concentrations (Figure 4). Significant effects of line (P<.02) and nutritional status (P<.01) were observed on GH concentrations. Pigs which had not nursed had

higher GH ($P < .01$) and IGFBP-2 concentrations than those which had nursed. Nursing also influenced circulating levels of IGF-I ($P<.001$) and IGF-II ($P<.01$). In contrast to the GH response, pigs which had not nursed had lower serum IGF-I and IGF-II concentrations than pigs which had nursed. In addition, a significant interaction ($P<.01$) of line on effect of nursing was noted for IGF-I, in that the effect of nursing on IGF-I in the obese pigs was negligible.

DISCUSSION

In the present study, the overall temporal pattern of circulating growth factor levels was characterized by distinct alterations in serum concentrations with postnatal age in both genotypes of swine. As previously reported in a commercial line of swine (22,23), GH concentrations were high at birth and declined rapidly during the neonatal period in both genetically lean and obese pigs. In general, serum levels of IGF-I, IGF-II and IGFBP-2 declined to some extent between birth and 7 days of age, but remained at a high level in the circulation in pigs of both genotypes during early postnatal growth. Pigs from the obese line had lower serum GH and IGF-I levels at birth and lower IGF-I concentrations during the first week of postnatal life. These lower levels of circulating growth factors may be in part responsible for or a reflection of the differing rates of growth, maturation, and body composition observed in the obese line *versus* the lean line both pre- and postnatally (11,12,13). Hausman et al. (24) measured changes in IGF-I and IGF-II associated with fetal growth in pigs of the obese line used herein and pigs of a lean commercial crossbred line. Serum levels of IGF-I and IGF-II increased with fetal age in fetuses of the commercial lean genotype. In contrast, this age-dependent increase in IGF-II was not apparent in fetuses of the obese genotype and serum levels of IGF-I were lower than in lean fetuses. The fact that the obese line fetuses had lighter organ and tissue weights throughout gestation supports the contention that the IGF peptides are important mediators of fetal and postnatal growth and development (25).

Following a precipitous decline in circulating GH concentrations during the early neonatal period, serum GH increased between 3 and 5 weeks of age, regardless of line. A similar rise in peripheral GH levels was described in crossbred boars with apex values at about 45 days of age (26). More recently, both basal and average daily plasma GH concentrations were reported to increase approximately 50% between 10 and 20 kg liveweight in both fast-growing and slow-growing lines of pigs (6). During this period, i.e., 3 to 5 weeks of age, the pituitary-gonadal axis becomes functional and in males the neonatal elevation in testosterone begins to wane (27,28). Thus age, and sex differences in peripheral GH concentrations may be related to the development of a functional hypothalamic-pituitary-gonadal axis.

Circulating IGF-II, as well as IGF-I levels, were relatively high in both lines of pigs during the postnatal period. This is in contrast to that observed in rats (29) and sheep (30) in which a developmental switch in the serum IGFs and IGFBP profile occurs during this time. In perinatal rats, the fetal serum profile characterized by high IGF-II and IGFBP-2 is replaced by a profile consisting of high IGF-I concentrations and elevated IGFBP-3 levels, accompanied by a sharp decline in IGFBP-2 levels and almost undetectable IGF-II concentrations (29,31). In both lean and obese lines of pigs, serum IGF-II and IGFBP-2 levels were relatively high during the neonatal period, and IGF-II concentrations were subsequently elevated further post-weaning. A developmental rise in circulating IGF-II during the post-weaning period has also been described in a crossbred line of pigs (6). In this regard, the pig is similar to the human which maintains elevated postnatal circulating IGF-II levels (32). Changes in circulating IGF-I and IGF-II concentrations did not appear to be related to peripheral GH secretion in either line of pig during the early period of postnatal growth. For example, the rise in mean serum GH levels between weeks 3 and 5 presented in Figure 1 was not accompanied by a concomitant elevation in mean serum IGF-I and IGF-II, nor was the peripubertal rise in mean serum IGF-II associated with an increase in serum GH. Owens et al. (6) found

no significant correlation between plasma GH and IGF-I, IGF-II, or IGFBPs in a fast-growing genotype of swine up to 35 kg body weight. This is consistent with the existence of a period of GH-independent IGF-stimulated growth in swine, as observed in rats (33,34). The rise in IGF-II concentration between weeks 12 and 22 was greater in amplitude and had a longer duration in the obese line pigs and male pigs overall. Interestingly, this period of time is associated with a number of pubertal changes. For instance, at this time of development the rate of increase in testicular and epididymal weight exceeds that of body weight in males (26). In addition, rapid increases in the development of seminiferous tubules, number of germ cells, and volume of Leydig cells occur during this period (35). Moreover, the hypothalamic-pituitary-gonadal axis becomes mature between 9 to 20 weeks of age in pigs (36,37). Finally, the onset of puberty, defined as the first standing estrus in the female, occurs at about 23 weeks of age. Thus, it is possible that this peripubertal rise in IGF-II concentration is associated with reproductive maturation processes. IGF-I and IGF-II have direct effects on the growth and differentiation of ovarian follicular cells in vitro (38,39,40) and are present in high concentrations in human Graafian follicles and granulosa cells (41), as well as porcine follicular fluid and testes (42,43).

Nutrient availability profoundly impacts circulating growth factor levels. In adult humans, IGF-I and IGF-II concentrations are reduced following fasting (44) or protein/calorie restriction (45,46). Malnutrition in neonatal suckling rats created by variation in litter size did not alter plasma GH concentrations, but reduced plasma IGF-I levels (47). We have previously reported that nutritional restriction over several hours results in the uncoupling of the GH-IGF axis in mature crossbred hogs (19,48). During nutritional restriction, elevated circulating GH concentrations were observed in crossbred neonatal pigs (23,49), concomitant with reduced serum levels of IGF-I (49). In the current study, the non-nursed piglets were sampled immediately after birth, rather than following several hours of a postnatal fast. Concentrations of IGF-I were increased following nursing in lean piglets, while nursing did not influence IGF-I concentrations in piglets of the obese line. This is consistent with the lower IGF-I levels observed in obese *versus* lean pigs during the first few days of neonatal life and may reflect a propensity towards slower growth and less lean tissue deposition. Pigs which were not nursed maintained higher serum GH and IGFBP-2 concentrations, but lower levels of IGF-II, regardless of line. Orlowski et al. (50) has shown that both IGFBP-2 mRNA and serum IGFBP-2 are increased in fasted rats. More recently, McCusker et al. (8) reported that neonatal pigs fasted for 48 hr have reduced serum levels of IGFBP-2 as detected by ligand blot analysis, but have levels which are four-fold higher when measured by RIA. In the present study, elevated levels of IGFBP-2 in the non-nursed pigs, in association with low levels of serum IGFs, might provide protection from the insulin-like effects of the IGF peptide, while maximizing their anabolic activity in the face of a limited nutritional environment.

Data from this study indicates that peripheral concentrations of growth factors are influenced by age and genotype of pigs selected for high and low fatness. Differences between lines appear to be particularly evident prior to parturition and during the first week of neonatal life. Pigs of the obese line appear to be deficient in specific growth factors during these times. Lower levels of growth factors in the obese pigs may in part be responsible for or a reflection of the slower growth, greater percent fat and lower percent lean tissue content that characterizes pigs of the obese line.

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[2] Mention of a trade name, proprietary product, or specific equipment does not constitute a guarantee or warranty by the U.S. Department of Agriculture and does not imply approval to the exclusion of other products that may be suitable.

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